Case Letter

Immediate oral amiodarone re-challenge following the development of parenteral-induced acute liver toxicity

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Dear editor,

Amiodarone is a class III antiarrhythmic medication commonly used in the emergency department (ED) and other critical care settings to treat several types of arrhythmias while also serving as a fixture of the Advanced Cardiac Life Support algorithm.[1] Its mechanism of action primarily involves blocking potassium channel currents during myocyte repolarization with additional effects on beta-adrenergic receptors and both sodium and calcium channel blockade.[2] One of amiodarone's less known complications is the development of acute hepatotoxicity with intravenous (IV) administration.[3] While discontinuation has been recommended, there is limited literature to help guide management when clinical factors warrant its continuation.

CASE

A 77-year-old female with a history of chronic obstructive pulmonary disease, hyperlipidemia, atrial fibrillation (AF), coronary artery disease with prior non-ST-elevation myocardial infarction (NSTEMI), and cardiac stent placement, presented to the intensive cardiac care unit (ICCU) after having another NSTEMI and subsequent acute decompensated heart failure. Prior to her arrival in the ICCU, she was started on oral amiodarone 400 mg every eight hours to manage her AF and atrial premature contractions. She had no evidence of hepatic dysfunction.

In the ICCU, the patient was started on non-invasive ventilatory support with continued episodes of AF and the rapid ventricular rate (RVR). She was subsequently started on amiodarone (150 mg IV bolus followed by 360 mg IV infusion at the rate of 1 mg/minute for six hours). The diluent concentrations included both the 1.5 mg/mL and the 1.8 mg/mL iso-osmotic solutions in dextrose formularies at different administrations of the medication. A second 360 mg amiodarone (IV infusion) was then followed at the rate of 0.5 mg/minute. These formularies didn't contain polysorbate 80 which was traditionally associated with hepatotoxicity in patients receiving IV amiodarone. On this regimen, the patient remained in normal sinus rhythm (NSR).

About eight hours after administering the IV amiodarone, the patient developed acute transaminase elevation. Her alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased from 35 U/L to 1,841 U/L and from 48 U/L to 2,777 U/L, respectively. Additionally, her international normalization ratio (INR) increased from 1.2 to 2.6. The platelet count was normal at $305\times10^3/\mu L$ and remained within normal limits throughout the period of suspected toxicity. Additional findings included alkaline phosphate 92 U/L, total bilirubin 1.3 mg/dL, and direct bilirubin 0.7 mg/dL. There was no other evidence of broader systemic organ dysfunction secondary to ischemia or hypoperfusion, including normal creatinine 0.61 mg/dL. A computed tomography (CT) of the abdomen and pelvis with contrast demonstrated a normal-size liver. There were no reported findings of contrast reflux into the hepatic or renal veins, layering of contrast in a dependent manner, or parenchymal enhancement in the dependent portion of the liver.[4] Because of the patient's history and acute nature of the isolated hepatic injury, no other infectious or serological

abnormalities were considered. Additionally, the patient had been hospitalized and intubated leading up to this period, and the toxic ingestion such as alcohol was not considered or tested for.

Initially, congestive hepatopathy was considered as the underlying pathophysiologic mechanism; however, Swan-Ganz findings after the patient's initial shock and two days prior to initiation of IV amiodarone administration, showed no evidence of sustained cardiogenic shock. The Swan-Ganz monitoring after the onset of the hepatopathy was also not consistent with refractory cardiogenic shock. Furthermore, the pattern of the patient's liver test abnormalities was not consistent with that commonly seen in congestive hepatopathy.[5]

With both an isolated hypertransaminemia and evidence of acute functional liver abnormality, the decision was made to discontinue amiodarone in its IV formulation. However, since there was a reluctance to anticoagulate and the patient had a history of bleeding, the decision was made to switch to oral amiodarone to maintain NSR and prevent the need for cardioversion in the context of interrupted anticoagulation.

The patient's INR trended down and returned to baseline within two days. In the four days after her initial transaminase elevation, her ALT and AST steadily improved from 1,841 U/L to 685 U/L and from 2,777 U/L to 532 U/L, respectively. The oral amiodarone effectively managed the patient's AF for the remainder of her ICCU admission. Unfortunately, the patient subsequently developed septic shock from toxic megacolon and bacteremia secondary to clostridium difficile infection. She developed multiorgan dysfunction and died on hospital day 21.

DISCUSSION

Despite its ubiquitous and clinically important role as a central antiarrhythmic agent, amiodarone's significant toxicity and side effect profile represent a considerable challenge to practitioners in the emergency and intensive care settings. The drug is available in two formulations: oral and IV. The oral pharmacology and its mechanism of hepatic metabolism, accumulation, and incidence of toxicity were described through a series of case reports and translational pathologic studies from the 1960s to the 1980s, and shown to have an injury pattern similar to that of alcohol-induced liver disease.[6,7] Although transient elevations in hepatic laboratory studies are common, the incidence of liver injury warranting the discontinuation of treatment is seen in roughly 1% of patients taking the oral formulation.[8] Generally, elevations in liver enzymes greater than twice the normal levels should prompt concern for true liver toxicity and warrant discontinuing the medication.

Over several decades, a series of case reports have highlighted the incidence of a rare (<0.01%) and unique type of acute liver injury secondary to the IV infusions of amiodarone.[9] Unlike the oral formulary, abnormalities are often seen within hours of administration and improved within weeks after discontinuing the medication.[10] This process is considered to have a unique mechanism attributed to either ischemic hepatitis, idiosyncratic toxicity, hypersensitivity, or toxicity of the vehicle (polysorbate 80) causing direct cell toxicity, free radical formation, and centrilobular necrosis.[11-13]

Since the early 2000s, several case reports have been published with accompanying literature reviews considering the relationship between IV amiodarone and liver toxicity. Rätz Bravo et al[12] reported a series of three cases while describing 25 additional cases dating back to 1986. In 2013, Nasser et al[13] presented one case report and a literature review of 33 previously reported cases (28 cases were previously reported by Rätz Bravo et al[12]). This report was the first to comprehensively review cases in which patients were able to be re-challenged with oral amiodarone without further compromising their acute liver injury.

Despite IV amiodarone's regular use in the ED setting, the emergency medicine literature is more limited. A case report out of an ED in Torino, Italy, described the acute development of transaminase elevation with evidence of functional liver toxicity secondary to parenteral administration of amiodarone. The decision was made to discontinue the medication leading to eventually resolution of liver injury.[14] A second case from the University of Genova reported an ED administration of IV amiodarone for acute arrhythmia, which subsequently led to the development of hepatic toxicity.[15] These two cases served to highlight the importance of this disease process in emergency and critical care practice.

When taken together, the existing case literature has enabled practitioners to develop broad definitions for understanding the presentation, management, and clinical course of this pathologic process. It is generally accepted that acute hepatotoxicity secondary to IV amiodarone develops within hours to days of the drug's initial administration. It is not uncommon for liver enzymes to rise as high as the thousands U/L, with or without the development of functional liver failure. Discontinuation of the infusion is the first-line treatment and often leads to complete liver recovery within a period of several days to weeks. There is, however, a considerable cohort of patients, who are secondary to initial hepatic insult or overall burden of comorbidities and are more at risk for developing this toxicity and have higher rates of mortality.[16]

It is unclear whether IV amiodarone-induced hepatotoxic patients could be re-challenged with the oral formulation of amiodarone. The most well-established theory for amiodarone's toxicity is that polysorbate 80, a diluent in the parenteral formulation, and not the iodinated benzofurane molecule itself, is the toxic culprit.[17] The hypothesis that an oral re-challenge of amiodarone is safe in case of IV amiodarone-induced hepatotoxicity, which was demonstrated in a case report by Rhodes et al.[17] It was further supported by Rätz Bravo et al[12] and Maker et al[18] in 2005. Both latter cases, however, had periods of 2–7 days where all forms of amiodarone were completely discontinued. Lahababi et al's case report in 2012 elected to restart oral amiodarone after their patient's liver was normalized. The authors concluded that patients who had developed acute liver toxicity from the IV formulary could be restarted on the oral medication after the resolution of hepatitis and under the stipulation that liver enzymes would continue to be closely followed.[19] Uniquely, our case report indicates that starting oral amiodarone immediately, even during the hepatotoxic recovery phase, is safe.

CONCLUSIONS

Acute hepatotoxicity secondary to IV amiodarone, a drug used commonly in the emergency and critical care settings, is an extremely rare clinical presentation. Through limited case reports over the last century, physicians are now beginning to better understand its presentation, pathologic process, and management. Our case, while further reinforcing the existing literature, sheds light on new areas that should be explored when considering the important question as to whether oral amiodarone can serve as a safe alternative after IV-induced hepatotoxicity. Uniquely, our case shows that oral amiodarone can be immediately restarted after parenteral dosing is stopped and can enable emergency and critical care physicians to continue the use of the drug's oral formulation to help manage refractory arrhythmias.

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